REVIEW

50th anniversary of the word "Allosteric"

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Abstract: A brief historical account on the origin and meaning of the word "allosteric" is presented. The word was coined in an attempt to qualify the chemical mechanism of the feedback inhibition of bacterial enzymes by regulatory ligands. The data lead to the proposal that, at variance with the classical mechanism of mutual exclusion by steric hindrance, the inhibition takes place through an "allosteric" interaction between "no overlapping", stereospecifically distinct, sites for substrate and feedback inhibitor, mediated by a discrete reversible alteration of the molecular structure of the protein.

Keywords: allosteric; allostery; biochemistry; pharmacological literature

Introduction

The word "allosteric" is widely used (944,000 hits on Google) in the biochemical and pharmacological literature as an adjective to qualify enzymes, receptors and proteins in general as well as sites and conformational transitions. The substantive "allostery" is less frequently used and in a more restricted sense: mostly to designate conformational transitions. The history and significance of the word "allosteric" is directly associated with the 1961 26th Cold Spring Harbor Symposium on Quantitative Biology entitled "cellular regulatory mechanisms." The word "allosteric" was not orally pronounced during the meeting. It appeared for the first time in the printed version of the Proceedings: in the General Discussion written by Monod and Jacob as a conclusion of the meeting. For once, a new word became popular even though its first appearance was in a printed form. This brief historical account on the origin and meaning of the word "allosteric" will be presented as a kind of conceptual evolution that encompassed a few singular highlights.

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Regulation of Cellular Metabolism by Feedback Inhibition

Biochemistry in the first 60 years of the 20th century mostly consisted of the identification of the main components of the living cell, its elementary metabolites, the principal enzyme reactions of intermediary metabolism, and their genetic characterisation as proteins. The extension to the cell of Claude Bernard's concept of constancy of the internal environment (*milieu intérieur*) and of its control (as for instance in glucose *homeostasis*) that was initially conceived for the whole organism, introduced the regulation of cellular metabolism as a fundamental topic of biochemical research. Enzyme adaptation in bacteria—the transient increase, or decrease, of enzyme production in response to a specific nutrient—became a model to investigate biological regulation at the gene level and was soon shown to result from a regulation of gene expression at the transcriptional level.[1] In parallel, the regulation of enzyme activity by covalent phosphorylation and dephosphorylation was demonstrated as a major alternate mechanism of metabolic regulation in higher organisms, specifically in the case of glycogen metabolism.[2,3] Also, in the 50s, the cybernetics and control theory perspective became influential in the

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understanding of metabolic regulation of living organisms, bacteria in particular, and was familiar to Jacques Monod. Quantitatively measuring the rates of amino acid synthesis in *Escherichia coli* (*E. coli*) with the chemostat, Novick and Szilard[4] revealed that the synthesis of the tryptophan precursor indole-3-glycerol phosphate is rapidly inhibited by added tryptophan. As a consequence, they postulated that an enzyme early in the pathway was feedback-inhibited by the end product of the biosynthetic chain. In parallel, Adelberg and Umbarger,[5] investigating the biosynthesis of another amino acid valine, noticed that in a valine-requiring mutant of *E. coli* the secretion of an intermediate of valine biosynthesis—alpha keto isovaleric acid—was inhibited by valine, the end product of the pathway. Umbarger[6] then discovered that, in cell free extracts, the first enzyme of the biosynthetic pathway of L-isoleucine, L-threonine deaminase was feedback-inhibited by L-isoleucine. A similar finding was reported by Yates and Pardee[7] for the pyrimidine biosynthetic pathway where the first enzyme, aspartate transcarbamylase, is feedback inhibited by the pyrimidine, cytidine triphosphate (CTP), that *E. coli* produces after a sequence of seven further reactions. Later, Earl Stadtman and George Cohen,[8] elucidating the original case of branched biosynthetic pathways of the amino acids threonine and lysine, discovered a dual feedback inhibition of the first step catalysed by aspartyl kinase by the two end products, threonine and lysine.

Figure 1. Editorial note: The author kindly provided this photo of himself taken around 1965. I also thank Dr. Maurizio Brunori for suggesting this commemorative review. B.W.M.

The Mechanism of Feedback Inhibition: Steric Hindrance or "No Overlapping"

The several examples of feedback inhibition of metabolic enzymes evidenced in the late 50s, all raised an interesting biochemical problem. What is the mechanism by which a regulatory metabolite strongly and specifically blocks the catalytic activity of an enzyme without showing an evident structural similarity with the enzyme substrate like, for instance, CTP and aspartate in the case of aspartate transcarbamylase? In addition, the early *in vitro* data with threonine deaminase revealed two rather unexpected features: an apparent competitive inhibition between feedback inhibitor and substrate and a sigmoid high order substrate-concentration relationship.[6]

These were the premises when I had the privilege to enter the field as a graduate student of François Jacob and Jacques Monod (Fig. 1). Among the several topics suggested by my thesis advisors, all of considerable interest, one suggested by François Jacob particularly attracted me for its mechanistic aspect and its broad biological implication: the issue was to follow up and explain Umbarger's results. I started with the first enzyme of the valine pathway—acetolactate synthetase—that Umbarger and Brown[9] had shown to be feedback inhibited by valine and with the help of François Jacob identified *E. coli* strains that excreted valine and were interpreted as having an acetolactate synthase no longer feedback-inhibited by valine. This was the first result of its type but was never published. Acetolactate synthase was in fact a difficult enzyme to work with and I switched to L-threonine deaminase with closer supervision by Jacques Monod. I confirmed Umbarger's *in vitro* experiments that L-threonine deaminase was apparently competitively inhibited by L-isoleucine and that it displayed high-order kinetics toward both its substrate and feedback inhibitor. But soon I noticed (end of 1959, beginning of 1960) that the sensitivity of enzyme preparations to L-isoleucine changed with time and progressively decreased, specifically in the course of purification. Heating the enzyme up to 55°C accelerated the process and resulted in a complete loss of sensitivity to L-isoleucine, without significant degradation of enzymatic activity. The effect was blocked by the chelator magnesium titriplex suggesting the implication of a heavy metal in the process. Moreover, parachloromercuribenzoate gave a similar effect in the absence of heat treatment. This "desensitization" of the enzyme caused not only a loss of L-isoleucine feedback regulation, but also the

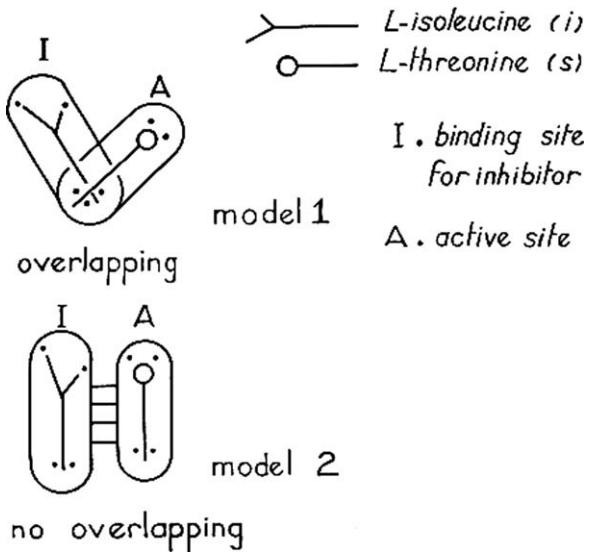

Figure 2. Two alternate models were presented in my communication at the 1961 Cold Spring Harbor Symposium in Quantitative Biology to account for the effect of the feedback inhibition by L-isoleucine on the bacterial enzyme L-threonine deaminase. Model 1 represents the classical mechanism of mutual exclusion by steric hindrance. Model 2, with "no overlapping" of the substrate binding site and of the binding site of the feedback inhibitor was selected as the most adequate to account for the data. In the general discussion of the Symposium, Monod and Jacob coined the word "allosteric" to qualify this second model.[10]

abolition of the unusual "bimolecular" kinetics of the enzyme toward its substrate. The complex cooperative kinetics of the enzyme thus seemed to be an integral part of the control system.

My results on L-threonine deaminase formed the content of the communication I presented orally in July 1961 at the Cold Spring Harbor meeting.[10] I briefly discussed the two obvious models which accounted for the paradoxical "competitive" antagonism between L-isoleucine and L-threonine (Fig. 2). According to the first model, the binding sites for the substrate and regulatory inhibitor are "partially overlapping" and the interaction is thus a classic competition by steric hindrance. In the second, novel, model, the two sites do not overlap—"no overlapping"—and the interaction takes place between topographically distinct sites. On the basis of the argument that desensitization is accompanied by a normalization of the kinetics, I favored the second model. I wrote in my communication "it seems inevitable to assume the existence of two distinct sites which we would respectively designate as activity site (A) and inhibition site (I) and to further assume that the properties of the active site are influenced by the compound bound at the inhibition site." A discussion with Jacques Monod then followed on the relationship between the non-hyperbolic shape of the substrate saturation curve and the inhibition by regulatory ligand. According to him, the partial structural analogy between threonine and isoleucine (both are amino acids) would allow the substrate to bind non specifically to the site of the inhibitor, and vice versa. I was not satisfied with this model but did not feel confident enough to present the alternate symmetrical one I had in mind (two active sites and two regulatory sites) against the views of my respected supervisor.

Immediately after my presentation at the Cold Spring Harbor Symposium, Bernard Davis stood up to make an important remark. According to him, "The properties of threonine dehydrase suggest an analogy to hemoglobin. Pauling has analyzed the mechanism by which each molecule of O_2 taken up by this compound affects its affinity for the next molecule of O_2. The four interdependent affinity constants of hemoglobin thus give rise to its characteristic sigmoid O_2 dissociation curve, so elegantly adapted to unloading a large fraction of its bound oxygen in the tissues without requiring an excessive drop in pO_2. Dr. Changeux's work suggests a similar mechanism, with two sites, to account for the sensitivity of a control enzyme in bacteria to the square of the concentration of its end product. The evolution of such similar mechanisms in a control enzyme and in hemoglobin should not be surprising, as the function of feedback inhibition, in stabilizing the concentration of a metabolite within a narrow range, has a certain resemblance to the function of hemoglobin" (p. 318). Hemoglobin was already becoming a prototype of regulatory protein.

Birthdate of "Allosteric Inhibition"

Jacques Monod gave the closing discussion of the meeting. In the section dealing with the regulation of enzyme activity, he cited extensively my results and included them in the general framework of feedback inhibition of cellular metabolism. He then mentioned that "closely similar observations have been made independently and simultaneously by Pardee (private communication) on another enzyme sensitive to end product (aspartate carbamyl transferase)" (see Gerhart and Pardee[11]). The phenomenon of end-product inhibition "where the inhibitor *is not a steric analogue of the substrate*" was referred to by Monod in his oral presentation as the "Novick-Szilard-Umbarger" effect, which he wrote on the blackboard as "NSU" effect. In Monod and Jacob's subsequent written publication, the statement appears "we propose to designate this mechanism (the NSU effect) as "allosteric inhibition" (pp 390–391). It was the "end product" -if I may say- of several open discussions in the laboratory during the writing of the paper by Jacques Monod in the fall 1961. This was the birth date of the word "allosteric" as composed of two Greek roots expressing the difference (allo-) in (stereo-) specificity of the two binding sites for

regulatory effector and for substrate.[12] It was further stated that the effect "need not be restricted to "end-product inhibition" which may turn out to constitute only one class of allosteric effects" (p. 391).

Both in the reference list of my communication[13] (p. 318) and in the text of Monod and Jacob the name of Daniel Koshland appears.[14] "Studies of the structure of the two sites and of their interaction, using analogs of the substrate and inhibitor, might conceivably lead to interpretations in terms of the "induced-fit" theory of Koshland[14]" (p. 391). Yet, Koshland's concern at the time was not the regulation of enzyme activity by a metabolic signal but the specificity of enzyme action. His view was that a "steric fit" seemed essential for the reaction to occur and that such a "fit occurred only after a change in shape of the enzyme molecule had been induced by the substrate" (Ref. [15], p. 475). We extended the idea of a "role of flexibility in enzyme action" to the indirect allosteric interaction between active site and regulatory site that would then be mediated by a reversible conformational change of the enzyme.

The Concept of "Allosteric Transition"

Subsequent work on L-threonine deaminase,[16] *aspartate transcarbamylase*[11] and other regulatory enzymes from eucaryotes, including glutamate dehydrogenase,[17] acetyl-CoA carboxylase,[18] phosphorylase b,[19] further substantiated the initial proposal of distinct sites for substrate and regulatory ligand that justified the word "allosteric". A general review entitled "Allosteric proteins and cellular control systems" was then written by Monod, Changeux and Jacob[20] with the aim to further specify "a general model schematizing the functional structures of controlling proteins". In this review the adjective allosteric is used in a much broader and more precise way than in the 1961 "General discussion", to the extent that Jacques Monod himself constantly referred to the 1963 review for the definition of the word "allosteric." It is used to qualify the site, the allosteric site complementary to the structure of another metabolite, the allosteric effector, which it binds specifically and reversibly. The formation of the enzyme-allosteric effector complex brings about a discrete reversible alteration of the molecular structure of the protein, an allosteric transition, which modifies the properties of the active site. The evidence that the allosteric effects do not directly participate in the reaction they control is emphasized. On the basis of observations on the activation of phosphorylase b by 5′AMP[19] and of glutamate dehydrogenase[17] by various effectors (ADP, diethylstilbestrol), a change in the state of aggregation of the protein is mentioned as a plausible mechanism for the allosteric transition. Yet, the question is raised as to whether or not "this alteration is induced directly by the binding of the nucleotide, the dimerisation being then a result of this primary effect" (p. 319). Still, in the general discussion, the "induced-fit" theory of Koshland is suggested (p. 323) as contributing to the allosteric transition.

In this review, Max Perutz's structural work on hemoglobin[21] is extensively discussed. Enough progress had been made with this system to be able to evaluate the extent of the changes that accompany oxygen binding. "Firstly, the oxygen binding sites, the hemes, are about 30 A apart. Affinity interactions between hemes are therefore allosteric interactions. Secondly, a comparison between the three-dimensional structures of oxygenated and reduced hemoglobin by Muirhead and Perutz[22] disclosed a relative displacement between subunits, minor (about 19% of the distance between subunits) but still significant." I had the opportunity to meet directly with Max Perutz in Paris at the time the review was written and he was amazed that at 5.5Å resolution "only the quaternary structure of hemoglobin did change upon oxygenation". I remember that I replied to him that "the tertiary structure of the globin chain must also change upon oxygen binding". The report of these results, then unpublished, in the 1963 review reveals our early interest in hemoglobin structure and more specifically in the relationship between subunits' tertiary conformation and the quaternary structure of regulatory proteins.

The discussion of the 1963 paper finishes with a generalization of the concept of allosteric proteins. These molecules would be the key component of any system of biological control from the regulation of bacterial enzymes activity to hormone action, the action of thyroxine and estrogens on the enzyme glutamic-dehydrogenase being the favored model. The hypothesis was put forward that gene repressors are also allosteric proteins "possessing two sites, one of which binds the operator, the other the (positive or negative) effector" (p. 328). In 1961, Jacob and Monod had thought that the repressor was a polyribonucleotide, but as a result of further development of the work on regulatory enzymes and the failure to identify the repressor as an RNA (see Ullmann[23]) the idea was abandoned.

From "Instruction" to "Selection"

In the 1963 paper, the "conformational alterations" mediating allosteric effects were "eventually expressed as a dissociation of the protein" though a note added in proof nuances this statement. Yet, the "conclusion that allosteric transitions frequently involve alterations of quaternary structure" remains an important outcome of the review, an issue that was subsequently specified in the 1965 Monod-Wyman-Changeux (MWC) model.[24] Furthermore, the "instructive" mechanism where the binding of the ligand *induces* "a detectable conformational alteration of the enzyme" and the reference to the induced

fit theory of enzyme action by Koshland[25] was explicitly discussed and a recent theoretical paper of Koshland[26] on regulatory interactions mentioned.

During 1962 and in the spring of 1963, I tried to experimentally test the possibility that a change in the state of aggregation of L-threonine deaminase takes place in the presence of the feedback inhibitor. However, centrifugation experiments did not give results similar to those cited for other regulatory proteins in the 1963 review. The sedimentation coefficient of L-threonine deaminase did not change in the presence of either the substrate or the allosteric effectors. I thus tried to destabilize the subunit organization of L-threonine deaminase by mixing the enzyme preparation with 1.5 M urea. An enzyme inactivation equilibrium was reached. Interestingly, the effectors of the enzyme modified it in a characteristic manner. The feedback inhibitor L-isoleucine caused reactivation of the urea-inactivated enzyme; the activator L-norleucine, L-valine and the substrate analog, L-allothreonine, enhanced inactivation that was interpreted as the dissociation of the enzyme into its inactive subunits. At the next 1963 Cold Spring Harbor Symposium, I presented these data[27] and proposed that "to the extent that the observations made in the presence of urea indicate that the activators or substrates tend to dissociate the molecule while the inhibitors tend to associate it, it may be surmised that the allosteric transitions involve weakening or increasing interactions between subunits. Such a situation is actually known in the case of hemoglobins (p. 503)".

Also, I remember, it came out of a discussion with Jacques Monod following the 1963 Cold Spring Harbor meeting, that to interpret the differential effect of ligands on L-threonine deaminase equilibrium in urea, the minimum hypothesis to consider was that the protein existed under only two discrete states: the allosteric activators would then stabilize the same state as the substrate; conversely, inhibitors would favor the other state. It was, in my opinion, the birth date of the concept of pre-existing conformational states, i.e., of a "selection" rather than an instruction mechanism by the ligands. It allowed a remarkable economy of means and simply explained a large number of kinetic properties of the native enzyme. Prior to the 1963 Symposium, I had collected a large body of kinetic data with L-threonine deaminase,[16,27] in particular the effect of heterotropic ligands on the cooperativity of substrate binding and their concomitant loss upon "desensitization" also noted by John Gerhart with aspartate transcarbamylase.[28,29] These data and interpretations contrasted with Koshland's hypothesis of a conformational change induced by the interaction with the ligand, leading to multiple structural states, each one adapted to the particular structure of the ligand. The concept of a preformed equilibrium between a few discrete conformations differentially stabilized by the effectors of the protein became one of the main statements of the MWC model that was initially thought to become a conclusion of my PhD thesis.[32,38]

In any instance, it is worth noting that the paradigmatic change from instruction to selection, arose, if I may say, from "the pressure of facts" rather than from any kind of ideological choice. These views have been very recently reformulated and discussed in terms of "conformational shift" or "shape shifting" by various groups.[30,31]

Conclusion

Because its birth date, the word "allosteric," which was initially coined to specify the mechanism of inhibition of bacterial regulatory enzymes by their feedback regulatory ligand, has been extended to the "indirect" interaction between topographically distinct sites mediated by a conformational change of a protein molecule. The concept first applied to metabolic control systems and genetic repressors by Monod, Changeux and Jacob[20] was extended, in the last chapter of my PhD thesis,[32] to "membrane phenomena which give rise, altogether, to the recognition of stereo-specific metabolic signals and to their transmission (such as synaptic transmission) (*–and which-*) might involve mechanisms analogous to those described with allosteric proteins". This notion was subsequently amplified and specified to take into account: 1) the integration of the neurotransmitter receptors into biological membranes and the various possible cooperative effects resulting from their integration[33–35] and 2) the "electrogenic" action of the neurotransmitter[33,35–37] in the case of the ligand-gated ion channels. In addition to these receptor-channels, the concept has received support from studies of other categories of receptors of major pharmacological importance,[38] such as the G-protein coupled receptors,[39–44] but also the nuclear receptors for various signals including hormones[45–47] thus generalizing the plausibility of the concept of allosteric interaction between topographically distinct sites to a broad variety of regulatory proteins in living organisms.

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